

REMARKS

This Reply is responsive to the Office Action mailed March 30, 2005. It is anticipated that the amendments and remarks contained herein should obviate all the outstanding rejections and objections, and place this case in condition for allowance.

Applicants confirm their Election of Group I, directed to an isolated nucleic acid sequence encoding a T2R76 polypeptide which is a member of the T2R family of bitter taste receptors, vectors containing, and isolated host cells transfected or transformed with such isolated T2R76 polypeptide encoding nucleic acid sequences. The restriction between the nucleic acid sequence (Group I) and the polypeptide group II was traversed previously on the basis that the searches are co-extensive. Applicants continue to believe that this is the case and should have been found sufficient particularly since many of the prior-examined claims specifically required the presence of the expressed T2R76 polypeptide. (See prior-examined claims 16-26 all of which require the T2R76 polypeptide be present.) These claims could not have been treated on the merits without considering the patentability of the T2R76 polypeptide. However, this restriction requirement is now moot because in order to expedite prosecution, claims 1-67 have been cancelled in favor of new claims 68 through 92. All of these claims correspond to the elected group (prior claims 1-3 and 16-26) as they are directed to isolated T2R76 nucleic acid sequences, host cells or vectors containing.

Applicants note that all of the newly submitted claims find explicit or implicit support from the as-filed specification including the original claims.

Turning now to the Office Action, claims 1-3 and 16-26 are examined and the remaining claims 4-15 and 27-67 withdrawn from consideration as being directed to a non-elected invention. As noted above new claims 68-92 correspond to previous claims 1-3 and 16-26. These claims have been rewritten in an effort to overcome all the outstanding rejections and objections.

The specification stands objected to based on informalities in paragraph [00033]. These objections are believed to be cured by the substitute paragraph [00033] contained in this Amendment.

Claims 1-3 and 16-26 stand rejected under 35 USC §101 as assertedly not being supported by a specific and substantial asserted utility. Applicants strenuously traverse this rejection based on at least the following.

Firstly, the as-filed specification provides substantial information which would be sufficient for one skilled in the art to reasonably conclude that the novel gene identified by the present inventors is a member of the human T2R taste receptor family which constitute a family of G protein coupled receptors which share related structural and functional characteristics and play an active role in human bitter taste transduction.

For example, the as-filed specification discloses that the claimed T2R76 nucleic acid sequence encodes a member of a family of GPCRs sharing a variety

of common properties including the following: (i) encode GPCR proteins having a conserved structure across different members of the family (ii) are specifically expressed in a subset of taste receptor cells of the tongue and palate epithelia (Adler et al., 2000; Chandrashekar et al., 2000; Matsunami et al., 2000); (iii) are genetically linked to loci linked to bitter taste in both humans and rodents (Connelly et al., 1976; Capeless et al., 1992; Reed et al., 1999; Adler et al., 2000); (iv) activate gustducin in vitro, which is known to be a G protein specifically expressed in taste cells and is moreover linked to bitter taste transduction (gustducin activation occurs selectively in response to the presence of bitter ligands).

Secondly, this patent application incorporates by reference prior published patent applications by Zuker et al. including WO 01/18050 and WO 01/77676 and an article by Chandrashekar et al. Cell 100 :703-711 (2000) which contain experimental data substantiating that several members of the T2R family including mT2R5 and mT2R8 encode functional taste receptor polypeptides that specifically respond to bitter ligands. As further evidence that the subject application is enabling, Applicants further note that the present Assignee has de-orphaned about a dozen T2R sequences which are claimed in Applicants' earlier T2R patent applications incorporated by reference in this application using the same assay methods disclosed herein (as well as in Applicant's earlier patent applications) This reproducibility confirms Applicants' reasonable expectations, namely that members of the T2R family such as hT2R76 encode

bitter taste receptor polypeptides which specifically respond to bitter ligands at concentrations which parallel the bitter taste thresholds for these bitter taste ligands in human subjects. Particularly, the Examiner is respectfully referred to the experimental data and supporting claims in US Serial No. 10/191,058 filed by the present Assignee on July 10, 2002 which provides experimental data establishing that 3 human T2Rs cloned by the present assignee Senomyx encode functional bitter taste receptors that specifically respond to bitter ligands. Additionally, the attention of the Examiner is respectfully directed to a recently filed provisional application by the assignee; US Provisional Application 60/650,555 filed on February 8, 2005 which contains functional data showing that another 7 human T2Rs cloned by the Assignee respond specifically to bitter compounds including strychnine, ranitidine, strychnine and denatonium. Therefore, in contradistinction to the position taken by the Examiner, there is substantial evidence and reason to believe that the genus of T2Rs cloned by the Assignee including T2R76 encode functional bitter taste receptors, and that this can be readily confirmed using the assay systems disclosed herein. Indeed, the prior success with other members of the family supports Applicant's position that the disclosed utility is credible and that obtaining proof of the disclosed utility (identification of specific bitter ligands that bind T2R76 polypeptide) would not require undue experimentation based on the extensive teachings of this application.

With respect to this point, the Office Action alleges that the as-filed specification “has given no indication as to which of these [bitter] compounds is expected to bind to and activate SEQ ID NO:2.” (See page 4, lines 9-10 of the Office Action). However, Applicants respectfully submit that this is incorrect. In fact, Example 5 at page 72 of the as-filed specification specifically teaches that binding assays using cell lines which express SEQ ID NO:2 may be screened against a set of bitter compounds (6 in total) as a means to confirm that hT2R76 is a bitter taste receptor. The specifically named bitter compounds in Example 5 include 6-n-thiouracil (PROP) (PROP is a well known bitter ligand that has bitter taste thresholds of 0.01 mM in PROP human tasters). As anticipated functional assays conducted using these compounds screened against T2R76 expressing HEK-293 cell lines have confirmed that the polypeptide contained in SEQ ID NO 2 specifically responds to PROP as well as a bitter alkaloid ligand found in Strychnos seeds. (This functional data is contained in a §132 Affidavit provided herewith and also is contained in a CIP patent application claiming priority to this application which was recently filed.) Applicants respectfully submit that this functional data along with the information contained in this and Applicants earlier T2R patent applications is convincing evidence that the as-filed specification provides a substantial and credible utility for the claimed isolated T2R76-encoding nucleic acid sequence, namely that it encodes a human bitter taste receptor. Based on the foregoing, withdrawal of the §101 rejection is respectfully believed to be in order.

Prior claims 1-3 and 16-26 were further rejected on 35 USC §112 first paragraph enablement grounds. The basis of the rejection is substantially overlapping with the basis for the §101 rejection. Essentially, the Examiner concludes that the as-filed specification does not enable one how to use the subject receptor polypeptides commensurate in scope with the claims. This rejection similarly hinges on the Examiner's assertion that the as-filed specification does not sufficiently or credibly establish that T2R76 is a human bitter taste receptor and further does not provide sufficient information to allow one skilled in the art to identify a bitter ligand that specifically binds hT2R76 "absent undue experimentation". This rejection is respectfully traversed for the same reasons as the §101 rejection above.

Particularly, for the reasons discussed above the subject application does contain extensive evidence and further cites numerous non-patent and patent documents in support of their identification of hT2R76 as a member of the human T2R taste receptor family. Additionally, while the burden is on the Patent Office to substantiate an enablement rejection, no evidence or convincing scientific reasoning has been set forth which would raise doubt as to the identity of T2R76 as a bitter taste receptor. Contrary to the Office Action, the Chandrashekar reference relied on by the Examiner to support the rejection is actually supportive of Applicant's claims since it contains functional data showing that a member of the T2R family (mT2R5) functions as a bitter taste receptor and specifically responds to a bitter ligand. In the Office Action the

Examiner seems to suggest that the data in the Chandrashekar reference (the reference de-orphaned 1 of 11 screened T2Rs tested) provides a reasonable inference that other T2Rs and T2R76 in particular may not encode functional taste receptors. However, Applicants maintain that the information in this and Applicants' other patent applications discussed above refute this supposition as they establish that many T2Rs have been proven to specifically respond to bitter ligands using the same assay and expression methods disclosed herein. (See for example US Serial No 10/191,058 and the provisional application discussed above.)

Moreover, with particular respect to the efficacy of hT2R76, the as-filed specification (Example 5) specifically teaches (and constructively reduces to practice) that the subject T2R76 receptor polypeptide may be tested in functional assays against 6 well known bitter ligands (including PROP) in order to confirm that hT2R76 is a bitter taste receptor. As substantiated by the §132 Affidavit of Dr. Mark Zoller provided herewith, this constructive reduction to practice been subsequently been actually reduced to practice as evidenced by the functional data contained in the Zoller Affidavit which confirms that T2R76 specifically responds to PROP (as well as to a bitter strychnine derived alkaloid). Thus, Applicants have provided convincing evidence that the specification provides an enabling disclosure based on the fact that the specification teaches assay systems as well as identifying a specific bitter ligand which have been successfully

reduced to practice using the methods and materials disclosed in this application and which have confirmed that hT2R76 is a bitter taste receptor.

Applicants also note with respect to the “scope” aspect of the invention that the claims have been drafted in a manner that is commensurate with the specific teachings in Applicant’s specification. Particularly, the current claims which encompass isolated nucleic acid T2R76 sequences that encode a polypeptide that differs from the T2R76 polypeptide contained in SEQ ID NO 2, require either (i) that the nucleic acid sequence hybridize under defined high stringency conditions to SEQ ID NO 1 AND encode a taste receptor that specifically binds a bitter ligand that also specifically binds to SEQ ID NO:2; or (ii) that the isolated nucleic acid sequence encode a polypeptide having high sequence identity to SEQ ID NO 2 (at least 90%) and that the polypeptide specifically bind to a bitter ligand that specifically binds SEQ ID NO:2.

It would be within the skill in the art, based on the teachings in this application, to identify isolate nucleic acid sequences that specifically hybridize to SEQ ID NO:1 under the recited high stringency conditions or to obtain isolated nucleic acid sequences that encode polypeptides at least 90% identical to SEQ ID NO:2; express such sequences using the disclosed methods and materials; and select using the disclosed assay methods those sequences which specifically bind a bitter ligand also specifically bound by SEQ ID NO:2 such as PROP. Applicants further respectfully submit that the scope of the pending claims is entirely consistent with the claims of many other gene patents in

instances as herein wherein the Patentees have cloned a novel gene, disclosed its function, and provided reproducible assay methods for selecting functional variants thereof.

In addition, it should be noted that the current claims only embrace isolated cells and do not encompass gene therapy. Finally, while several dependent claims provide for the subject T2R to be expressed in association with another T2R polypeptide, this phrase is not unduly broad as it properly should be construed based on the teachings of this application and the state of the art. Based on the extensive number of T2Rs cloned and publicly disclosed prior to the filing of this application, one skilled in the art would readily be able to select and express another T2R nucleic acid sequence in association with T2R76 absent the exercise of undue experimentation.

Based on the foregoing, Applicants respectfully submit that all of newly presented claims 68-92 are adequately enabled by the teachings of this application. Withdrawal of the 35 USC §112 enablement rejection is therefore respectfully requested.

Claims 1-3 and 16-26 were further rejected under 35 USC §112 first paragraph, on the basis that the as-filed specification does not establish that the inventors were in possession of the invention (isolated nucleic acid sequences encoding a human bitter taste receptor polypeptide.) This rejection is respectfully traversed for the same reasons as the §101 and §112 enablement rejections above. For the reasons set forth above, the as-filed specification

unequivocally provides sufficient information to reasonably conclude that Applicants were in possession of isolated nucleic acid sequences that encode a human bitter taste receptor polypeptide that specifically responds to bitter ligands including PROP in binding assays. Again the attention of the Examiner is respectfully directed to Example 5 which constructively reduces to practice assay methods using bitter ligands (including PROP) which have been later actually reduced to practice and have shown that T2R76 is specifically responsive to PROP. It is not necessary that a patent application contain data to establish "possession" of the invention under 35 USC 112 first paragraph. Rather the applicable legal test is would the specification teachings (which may include prophetic examples) reasonably place one skilled in the art in possession of the invention? This burden has been abundantly satisfied for the reasons enumerated above in the traversal of the 35 USC §101 and §112 rejections.

The Examiner further indicates with respect to this rejection that the rejected claims embrace a genus of sequences without reciting any common structural and functional characteristics to establish possession of the genus in accordance with the two-prong structure-function written description test laid out by the Federal Circuit in *Regents of California v Eli Lilly & Co.*, 119F3d 1559,1569, 43 USPQ2d 1398, 1406 (Fed Cir. 1997) However, it is respectfully submitted that this rejection should not be applicable against any of the newly submitted claims. As noted above, all of the newly submitted claims are directed to sequences having highly related structures (based on requirement that they

hybridize to SEQ ID NO:1 under highly stringent conditions and/or that they encode a polypeptide having at least 90% sequence identity with SEQ ID NO:2.) Thus the first part of the Eli Lilly test is satisfied with respect to all of the new pending claims because the claimed genus of nucleic acids possess a conserved structure.

Likewise, the second prong of the Eli Lilly test is satisfied since all of the newly submitted claims require that this genus of structurally conserved nucleic acids encode a taste receptor polypeptide that retains the functional properties of the endogenous T2R76 polypeptide as it must encode a polypeptide that specifically binds a bitter ligand that is specifically bound by the native T2R76 polypeptide (SEQ ID NO:2). For the same reasons enumerated above, the teachings of the application would place one skilled in the art in possession of assay methods which could be used to select nucleic acid sequences that meet these criteria, e.g., encode T2R76 variants which like T2R76 specifically bind and respond to PROP.

Therefore, the §112 written description rejection should not be maintained against any of the current claims.

Claims 1-3 and 16-26 were further rejected under 35 USC §112 second paragraph as assertedly being indefinite . The specific bases of the rejection are not addressed herein as the new claims do not contain the phraseology that was asserted to be unclear.

Claims 1-3 stand rejected under 35 USC §102 (a) based on a publication by Miwa WO200257309-A1 that occurred on July 25, 2002. This rejection is overcome by an Affidavit by the undersigned which establishes that Applicants were in possession of the claimed isolated hT2R76 sequence prior to the publication date of this patent disclosure. Withdrawal of this rejection is therefore respectfully requested.

Claims 16-22 further stand rejected under 35 USC §103 based on the same Miwa disclosure in view of Fuji et al, US Patent 5,763,218. Fuji is cited based on its disclosure relating to expression of a GPCR in a heterologous expression system. Based thereon the Examiner concludes that it would have been obvious to have expressed the sequence of Miwa using the methodology of Fuji et al.

This §103 rejection is obviated by the 131 Affidavit which effectively removes Miwa as a reference. Absent this reference, the expression of T2R76 would not have been obvious.

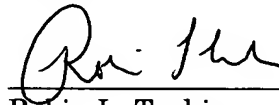
Claims 23-25 also stand rejected under 35 USC §103 based on Miwa in view of Fuji et al (Id) and US Patent 6,004,808 by Negulescu et al. This patent is cited based on its disclosure relating to the expression of promiscuous proteins in association with a GPCR. This rejection is also believed to be obviated by the Affidavit which effectively removes Miwa as a reference. Absent this reference, there would exist no motivation to express the subject T2R76 polypeptide using the Fuji expression system or the promiscuous G protein of Negulescu et al. Withdrawal of the §103 rejection of claims 23-25 is respectfully requested.

Based on the foregoing this application is believed to be in condition for allowance. A Notice to that effect is respectfully solicited. If the Examiner has any questions concerning this application, he is respectfully requested to contact the undersigned so that prosecution may be expedited.

If necessary to effect a timely response, this paper should be considered as a petition for an Extension of Time sufficient to effect a timely response, and please charge any deficiency in fees or credit any overpayments to Deposit Account No. 04-1679 (Docket #T1530-00094).

Respectfully submitted,

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Robin L. Teskin
Registration No. 35,030

DUANE MORRIS LLP
1667 K Street, N. W., Suite 700
Washington, DC 20006
Telephone No.: (202) 776-7800
Facsimile No.: (202) 776-7801

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